EphA4 as an effector of Twist1 in the guidance of osteogenic precursor cells during calvarial bone growth and in craniosynostosis.

Journal: Development

Publication Year: 2009

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PubMed link: 19201948

Funding Grants: CIRM Stem Cell Biology Training Grant

Public Summary:

Scientific Abstract:
Heterozygous loss of Twist1 function causes coronal synostosis in both mice and humans. We showed previously that in mice this phenotype is associated with a defect in the neural crest-mesoderm boundary within the coronal suture, as well as with a reduction in the expression of ephrin A2 (Efna2), ephrin A4 (Efna4) and EphA4 in the coronal suture. We also demonstrated that mutations in human EFNA4 are a cause of non-syndromic coronal synostosis. Here we investigate the cellular mechanisms by which Twist1, acting through Eph-ephrin signaling, regulates coronal suture development. We show that EphA4 mutant mice exhibit defects in the coronal suture and neural crest-mesoderm boundary that phenocopy those of Twist1(+/-) mice. Further, we demonstrate that Twist1 and EphA4 interact genetically: EphA4 expression in the coronal suture is reduced in Twist1 mutants, and compound Twist1-EphA4 heterozygotes have suture defects of greater severity than those of individual heterozygotes. Thus, EphA4 is a Twist1 effector in coronal suture development. Finally, by DiI labeling of migratory osteogenic precursor cells that contribute to the frontal and parietal bones, we show that Twist1 and EphA4 are required for the exclusion of such cells from the coronal suture. We suggest that the failure of this process in Twist1 and EphA4 mutants is the cause of craniosynostosis.